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**NO DRAWINGS**

*SEE ALSO COMPLETE SPECIFICATION*



**NEW ZEALAND**

***Patents Act 1953***

**PROVISIONAL SPECIFICATION**

Title: **Anthelmintic Formulations**

I/We, : ***Ancare Distributors Limited***
Address : 48 Diana Drive, Glenfield, Auckland, New Zealand
Nationality : New Zealand
do hereby declare this invention to be described in the following statement :



PF04.JWP

FEE CODE - 1040

## ABSTRACT

This invention relates to anthelmintic compositions and has particular application to compositions containing praziquantel (a pyrazinoisoquinoline derivative; *(2(Cyclohexylcarbonyl))-1,2,3,6,7,-11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one*) together with at least one other anthelmintic. A method of manufacture, and a method of administration for a composition incorporating praziquantel and levamisole is given.

## FIELD

This invention relates to pharmaceutical compositions for the treatment of helminthiasis in warm-blooded animals, more particularly cattle, sheep, goats, and other domesticated herbivores.

Helminthiasis is a widely occurring disease in farmed animals. It commonly causes clinical disease and has significant adverse economic effects on farming economies when present at subclinical levels. Over the past twenty-five years a number of initially successful anthelmintic agents, with relatively specific effects on the metabolism of smaller or larger groups of endoparasites have been discovered, trialled, and used successfully to control helminthiasis on farms. Various groups of compounds have a greater or lesser spectrum of activity - that is to say they are able to destroy a wider or smaller range of parasite. For example, the widely used "ivermectin" is active against parasitic roundworms and also against some ectoparasites, yet it is inactive against tapeworms because of a difference in their biochemical constitution. "Triclabendazole" is active only against the liver fluke *Fasciola hepatica*.

Unfortunately, resistance to the effects of particular compounds or related families has usually developed with time, after repeated use of the same compound, and has become one of the major problems in the use of these anthelmintic agents. In fact, the growth of drench resistance seems to be overtaking the ability of scientists to develop new drenches.

There is a need, therefore, for alternative anthelmintic formulations having the breadth of activity of the benzimidazole drugs (for example) but which slows the advancement of drench resistance.

## OBJECT

It is an object of this invention to provide novel pharmaceutical compositions having anthelmintic activity.

In one aspect the invention shall comprise a composition including an effective amount of the anthelmintic praziquantel together with effective amounts of at least one other anthelmintic.

Preferably the other anthelmintic is selected from the group comprising the avermectins; levamisole; tetramisole; or a substituted benzimidazole carbamate.

Praziquantel (published in New Zealand as Patent No. 176193) has for many years been used to control cestode infestations and schistosomiasis in humans. The surprising discovery that the efficacy of praziquantel can be enhanced in domesticated animals by simultaneous administration with other anthelmintics has been exploited in the present invention, which offers improved efficacy in the control of cestodes, together with simultaneous control of nematode infestations.

Examples of suitable benzimidazole drugs include drugs such as mebendazole, fenbendazole, oxfendazole, albendazole, cambendazole, parbendazole, oxibendazole, flubendazole and cyclobendazole.

Preferably, in the case of compositions incorporating levamisole, the composition has a pH less than 4.0 and in the most preferred aspect the pH is about 3.0.

Optionally, the composition may contain other veterinary products (including other anthelmintics).

A further aspect is to provide a method for treating helminthiasis in animals with compositions comprising praziquantel and at least one other anthelmintic.

Since praziquantel is a relatively insoluble material, we have devised formulations for administration in the form of drenches and examples are included in this specification.

We have previously found that combining benzimidazole drenches with levamisole drenches results in an unstable product due to the different pH values needed to maintain the stability of the individual products. Mixtures of levamisole as the hydrochloride together with praziquantel are stable, provided that the pH of the mixture is lower than approximately 4.

These and other aspects of the invention, which will be considered in all its novel aspects, will be apparent from the following description, which is given by way of example only.

A typical formula for this invention would include the following active ingredients:

| | |
|---|---|
| praziquantel drug | active in a range of activity from 0.5 - 15% w/v |
| AND | |
| A benzimidazole drug | active in a range of activity from 1 - 15% w/v |
| OR | |
| Levamisole | active in a range of activity from 1 - 10% w/v |
| OR | |
| ivermectin | active in a range of activity from 0.05 - 1% w/v |
| OR | |
| moxidectin | active in a range of activity from 0.05 - 1% w/v |
| OR | |
| doramectin | active in a range of activity from 0.05 - 1% w/v |

and one or more of the following ingredients to enhance stability and characteristics of the composition:

viscosity agents
surfactants
sanitizers
acidifiers
stabilizers

**EXAMPLE 1:**

Praziquantel/Levamisole HCl Drench

pH of 3.4 Density at 20 °C = 1.025 kg/l
Viscosity @ 20 °C = 20 sec. (Ford no. 4 cup)

| *Ingredient* | % w/w | % w/v |
|---|---|---|
| Water (hot) | 2.0 to 100 ml | |
| Polyoxystearate | 2.50 | 0.185 |
| PEG 6000 | 3.00 | 2.060 |
| praziquantel | 1.25 | |
| Defoamer RD | 0.20 | 0.206 |

| | | |
|---|---|---|
| Water (cold) | to 100 ml | |
| Potassium sorbate | 0.18 | |
| Citric Acid (anhyd) | 0.30 | 0.299 |
| Levamisole HCl | 3.75 | 3.863 |
| Keltrol | 0.20 | 1.030 |
| Mono propylene glycol | 0.40 | |
| Aerosil 200 | 1.00 | 1.030 |
| Formalin | 0.20 | 0.206 |
| | 100.00 | 100.000 ml |

We have found that it is possible to make an acidified praziquantel drench in which the stability of levamisole can be maintained without affecting the praziquantel component. The acidity of the resulting product is preferably of a pH of less than 4.0, preferably around 3.0. A lower pH down to 2.0 is preferable if minerals are added to the drench. We have found that the pH of the above examples will vary slightly on a batch by batch basis.

Manufacturing Instructions for Composition of Example I

1. Praziquantel premix - measure the hot water into a premix vessel, add the PEG 6000 and polyoxystearate 40 and mix until fully melted (approximately 65°C). Use external heating if required. Add the praziquantel and Defoamer RD and silverson until smooth and lump free.

2. Measure the bulk of the cold water into the production tank, add the potassium sorbate, citric acid, and levamisole hydrochloride and stir to dissolve.

3. Add the hot praziquantel premix to the production tank and stir until fully dispersed and lump-free.

4. Premix the Monopropylene glycol and Keltrol, add to the batch and silverson until dispersed and until the viscosity has fully developed.

5. Add the Aerosil 200 and silverson until fully dispersed.

6. When the batch temperature is below 40°C add the formalin and stir to dissolve.

7. Add the remaining water to make up to volume.

8. Take a test sample for laboratory analysis.

The procedure called "silversoning" is essentially mixing or dispersing in a device providing high shear rates within the fluid.

**EXAMPLE 2:**

Praziquantel/albendazole drench

By way of a second embodiment, a combination with an albendazole would be prepared using the following constituents:

| | % w/v |
|---|---|
| Water (hot) | 2.00 |
| PEG 6000 | 2.50 |
| Polyoxystearate 40 | 3.00 |
| Albendazole | 2.38 |
| Defoamer RD | 0.20 |
| Praziquantel | 2.50 |
| Water (cold) to volume | |
| Potassium sorbate | 0.18 |
| Citric acid | 0.30 |
| Keltrol | 0.20 |
| Monopropylene glycol | 0.40 |
| Formalin | 0.20 |
| Aerosil 200 | 1.00 |
| | 100 ml |

The pH of such a suspension is expected to be in the range of from 3.5 to 5.5.

Combinations with other benzimidazole-type compounds can be formulated in a manner similar to that of Example 2.

**EXAMPLE 3:**

Praziquantel/ivermectin drench

Combinations with avermectin-related compounds can be made as non-aqueous or aqueous suspensions depending on the stability of the avermectin compound. For example, a formulation including ivermectin and Praziquantel could be:

| | % w/v |
|---|---|
| ivermectin | 0.1 |
| Praziquantel | 1.88 |
| Propylene glycol | 40.00 |
| Water | to 100% |

The suspension would have a neutral pH.

Other avermectins such as doramectin or moxidectin may be used in place of ivermectin.

It is also possible to prepare a solution of praziquantel with appropriate organic solvents.

The resulting product is not only stable but also allows the farmer to obtain control of a wider range of parasites.

In addition, it is possible to include in the composition other veterinary products including ectoparasiticides, as well as other endoparasiticides, minerals, and trace elements as required.

The composition may be administered to mammals preferably by mouth as a drench, and as a single dose.

Finally it will be appreciated that various other alterations and modifications may be made to the foregoing without departing from the scope of this invention.

IMOTEC

**JAMES W PIPER & CO.**
Attorneys for the applicant
***ANCARE DISTRIBUTORS LIMITED***

Patents Form # 5

NEW ZEALAND

*Patents Act 1953*

COMPLETE SPECIFICATION

AFTER PROVISIONAL NO : 237086

DATED : 12 FEBRUARY 1991

TITLE : **Anthelmintic Formulations**

We, ***Ancare Distributors Limited***, a New Zealand company, of 48 Diana Drive, Glenfield, Auckland, New Zealand, hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement :



PF05.JWP

237086

## ABSTRACT

This invention relates to anthelmintic compositions and has particular application to compositions containing praziquantel (a pyrazinoisoquinoline derivative; *(2(Cyclohexylcarbonyl))-1,2,3,6,7,-11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one*) together with at least one other anthelmintic. Formulations are described containing: (i) praziquantel and levamisole, (ii) praziquantel and albendazole, (iii) praziquantel and oxfendazole, (iv) praziquantel and moxidectin, (v) praziquantel and ivermectin. The avermectin component may be replaced by Milbemycin D, or other milbemycins.

## FIELD

This invention relates to pharmaceutical compositions for the treatment of helminthiasis in warm-blooded animals, more particularly cattle, sheep, goats, and other domesticated herbivores.

## BACKGROUND

Helminthiasis is a widely occurring disease in farmed animals. It commonly causes clinical disease and has significant adverse economic effects on farming economies when present at subclinical levels. Over the past twenty-five years a number of initially successful anthelmintic agents, with relatively specific effects on the metabolism of smaller or larger groups of endoparasites have been discovered, trialled, and used successfully to control helminthiasis on farms. Various groups of compounds have a greater or lesser spectrum of activity - that is to say they are able to destroy a wider or smaller range of parasite. For example, the widely used "ivermectin" is active against parasitic roundworms and also against some ectoparasites, yet it is inactive against tapeworms because of a difference in their biochemical constitution. "Triclabendazole" is active only against the liver fluke *Fasciola hepatica*.

Unfortunately, resistance to the effects of particular compounds or related families has usually developed with time, after repeated use of the same compound, and has become one of the major problems in the use of these anthelmintic agents. In fact, the growth of drench resistance seems to be overtaking the ability of scientists to develop new drenches. The spread of "sheep measles" (cysts of the *Taenia ovis* species of tapeworm) is one such problem.

There is a need, therefore, for alternative anthelmintic formulations having the breadth of activity of the benzimidazole drugs (for example) but which slows the advancement of drench resistance.

## OBJECT

It is an object of this invention to provide novel pharmaceutical compositions having anthelmintic activity.

In one aspect the invention provides a veterinary liquid anthelmintic composition suitable for administration to farm animals including a liquid carrier and an effective amount of the anthelmintic praziquantel together with an effective amount or amounts of at least one other anthelmintic selected from the group comprising the avermectins; milbemycins; levamisole; tetramisole; or a benzimidazole chosen from the group comprising mebendazole, fenbendazole, oxfendazole, albendazole, cambendazole, parbendazole, oxibendazole, flubendazole or cyclobendazole.

Praziquantel *(2(Cyclohexylcarbonyl))-1,2,3,6,7,-11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one)* has for many years been used to control cestode infestations and schistosomiasis in humans. The surprising discovery that the efficacy of praziquantel can be enhanced in domesticated animals by simultaneous administration with other anthelmintics (as listed above) has been exploited in the present invention, which offers improved efficacy in the control of cestodes, together with simultaneous control of nematode infestations.

Preferably, in the case of compositions incorporating levamisole, the composition has a pH less than 4.0 and in the most preferred aspect the pH is about 3.0.

Optionally, the composition may contain other veterinary products (including other anthelmintics).

A further aspect is to provide a method for treating helminthiasis in animals with a veterinary liquid composition of the type defined in the claims.

When administered to sheep or lambs we prefer to administer the composition as a drench having an effective amount of praziquantel in the range of 2 to 7.5 mg/kg of body weight, and more preferably about 4mg/kg of body weight of sheep. For lambs the dose rate of praziquantel can be reduced to about 2mg/kg of body weight.

JMP 23.6.93

Since praziquantel is a relatively insoluble material, we have devised formulations for administration in the form of drenches and examples are included in this specification.

We have previously found that combining benzimidazole drenches with levamisole drenches results in an unstable product due to the different pH values needed to maintain

the stability of the individual products. Mixtures of levamisole as the hydrochloride together with praziquantel are stable, provided that the pH of the mixture is lower than approximately 4.

These and other aspects of the invention, which will be considered in all its novel aspects, will be apparent from the following description, which is given by way of example only.

## GENERAL FORMULATION

A typical formula for this invention would include the following active ingredients:

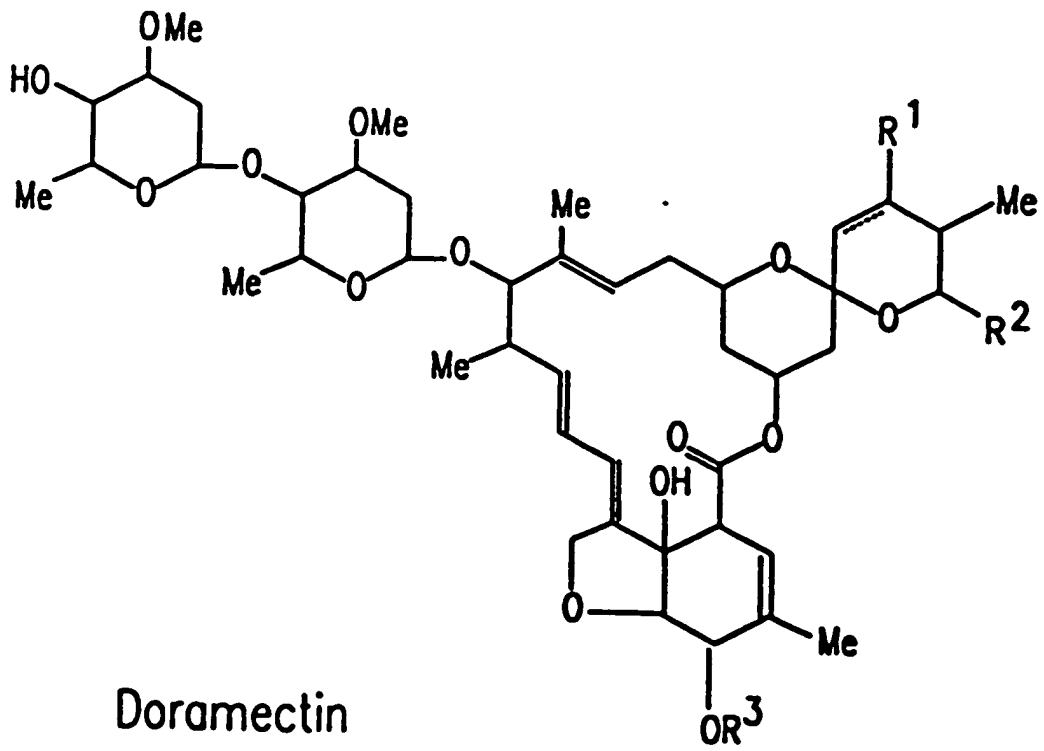
| | |
|---|---|
| praziquantel | active in a range of activity from 0.5 - 15% w/v |
| AND | |
| benzimidazole | active in a range of activity from 1 - 15% w/v |
| OR | |
| levamisole | active in a range of activity from 1 - 10% w/v |
| OR | |
| ivermectin | active in a range of activity from 0.05 - 1% w/v |
| OR | |
| moxidectin | active in a range of activity from 0.05 - 1% w/v |
| OR | |
| doramectin | active in a range of activity from 0.05 - 1% w/v |

and one or more of the following ingredients to enhance stability and characteristics of the composition:

viscosity agents
surfactants
sanitizers
acidifiers
stabilizers

Moxidectin [spiro(11,15-methano-2*H*m13*G*, 17*H*-furo (4,3,2-*pg*) (2,6) benzodioxacyclooctadectin-13,2' - (2H)pyran-7-one,20,20b-dihydroxy-6'-(1,3-dimethyl-T-butenyl)-4'-(methoxyimino)-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahydro-5',6,8,19-tetramethyl- (6R- (2a*Z*,4*E*,5'*S**,6*R**,6'*R**(*E*),8*E*,11*R**,13*S**,15*R**,17a*R**,20*R**,20b*S**)] is a new broadspectrum endectocide.

Doramectin is an avermectin whose structure is shown below.




Doramectin

**EXAMPLE 1:**

Praziquantel/Levamisole HCl Drench

pH of 3.4 Density at 20 °C = 1.025 kg/l
Viscosity @ 20 °C = 20 sec. (Ford no. 4 cup)

| *Ingredient* | *gm/100ml* |
|---|---|
| Water (hot) | 2.0 |
| Polyoxystearate 40USP/NF | 2.50 |
| PEG 6000* | 3.00 |
| Praziquantel | 1.88 |
| Defoamer RD | 0.20 |
| Water (cold) | to 100 ml |
| Potassium sorbate BP | 0.18 |
| Citric Acid (anhyd) BP | 0.30 |
| Levamisole HCl BP | 3.75 |
| Xanthan Gum USP/NF | 0.20 |
| Mono propylene glycol BP | 0.40 |
| Colloidal anhydrous silica BP | 1.00 |
| Formalehyde solution BP | 0.20 |
| | 100.00 |

*PEG 6000 is an abbreviation for Polyethylene Glycol 6000 USP/NF.

We have found that it is possible to make an acidified praziquantel drench in which the stability of levamisole can be maintained without affecting the praziquantel component. The acidity of the resulting product is preferably of a pH of less than 4.0, preferably around 3.0. A lower pH down to 2.0 is preferable if minerals are added to the drench. We have found that the pH of the above examples will vary slightly on a batch by batch basis.

Manufacturing Instructions for Composition of Example 1

1. Praziquantel premix - measure the hot water into a premix vessel, add the PEG 6000 and polyoxystearate 40 and mix until fully melted (approximately 65°C). Use external heating if required. Add the praziquantel and Defoamer RD and silverson until smooth and lump free.

2. Measure the bulk of the cold water into the production tank, add the potassium sorbate, citric acid, and levamisole hydrochloride and stir to dissolve.

3. Add the hot praziquantel premix to the production tank and stir until fully dispersed and lump-free.

4. Premix the Monopropylene glycol and Xanthan Gum, add to the batch and silverson until dispersed and until the viscosity has fully developed.

5. Add the colloidal anhydrous silica and silverson until fully dispersed.

6. When the batch temperature is below 40°C add the formalin and stir to dissolve.

7. Add the remaining water to make up to volume.

8. Take a test sample for laboratory analysis.

The procedure called "silversoning" is essentially mixing or dispersing in a device providing high shear rates within the fluid.

**EXAMPLE 2:**

Praziquantel/Albendazole Drench

By way of a second embodiment, a combination with an albendazole would be prepared using the following constituents:

| | *gm/100ml* |
|---|---|
| Water (hot) | 2.00 |
| PEG 6000 | 2.50 |
| Polyoxystearate 40 | 3.00 |
| Albendazole | 2.38 |
| Defoamer RD | 0.20 |
| Praziquantel | 2.50 |
| Water (cold) to 100ml | |
| Potassium sorbate | 0.18 |
| Citric acid | 0.30 |
| Xanthan Gum USP/NF | 0.20 |
| Monopropylene glycol | 0.40 |
| Formalin | 0.20 |
| Colloidal anhydrous silica | 1.00 |
| | 100 ml |

The pH of such a suspension is expected to be in the range of from 3.5 to 5.5.

Combinations with other benzimidazole-type compounds can be formulated in a manner similar to that of Example 2.

**EXAMPLE 3:**

Praziquantel/Ivermectin Drench

Combinations with avermectin-related compounds can be made as non-aqueous or aqueous suspensions depending on the stability of the avermectin compound. For example, a formulation including ivermectin and praziquantel could be:

| | *gm/100ml* |
|---|---|
| Ivermectin | 0.1 |
| Praziquantel | 1.88 |
| Propylene glycol | 40.00 |
| Water | to 100ml |

The suspension would have a neutral pH.
Other avermectins such as doramectin or moxidectin may be used in place of ivermectin.
It is also possible to prepare a solution of praziquantel with appropriate organic solvents.
The resulting product is not only stable but also allows the farmer to obtain control of a wider range of parasites.

**EXAMPLE 4:**

Praziquantel/Oxfendazole

A combination with an albendazole would be prepared using the following constituents:

| | *gm/100ml* |
|---|---|
| Water (hot) | 2.00 |
| PEG 6000 | 2.50 |
| Polyoxystearate 40 | 3.00 |
| Oxfendazole | 2.265 |
| Defoamer RD | 0.20 |
| Praziquantel | 2.50 |

| | |
|---|---|
| Water (cold) | to 100ml |
| Potassium sorbate | 0.18 |
| Citric acid | 0.30 |
| Xanthan Gum USP/NF | 0.20 |
| Monopropylene glycol | 0.40 |
| Formalin | 0.20 |
| Colloidal anhydrous silica | 1.00 |
| | 100 ml |

**EXAMPLE 5:**

Praziquantel/Moxidectin

| | *gm/100ml* |
|---|---|
| Praziquantel | 2.0 |
| Moxidectin | 0.10 |
| Propylene glycol | 20.0 |
| Xanthan Gum USP/NF | 0.2 |
| Water | to 100 ml |
| | 100ml |

**EXAMPLE 6:**

Praziquantel/Ivermectin

| | *gm/100ml* |
|---|---|
| Praziquantel | 2.0 |
| Ivermectin | 0.08 |
| Ethanol | 20.0 |
| Propylene glycol | to 100ml |
| | 100 ml |

In addition, it is possible to include in the composition other veterinary products including ectoparasiticides, as well as other endoparasiticides, minerals, and trace elements as required. In the following trials reference will be made to the praziquantel/levamisole formulation of Example 1. In some of the trials the formulation of Example 1 may include minerals and trace elements.

The compositions may be administered to mammals preferably by mouth as a drench, and as a single dose.

**TRIALS**

The formulation of Example 1 has been shown in a series of New Zealand trials to be highly effective in controlling benzimidazole resistant roundworms and tapeworms in sheep.

While levamisole has been well researched for the control of helminths in sheep, there historically has been little information on praziquantel in the ovine. Thomas & Gonnert [Research in Veterinary Science (1978) 24, 20] report a high efficacy in the control of Moniezia spp at a dose of 2.5mg/kg, while other studies against liver tapeworm (Stilesia hepatica) demonstrated efficacy at 15mg/kg.

A recent study by C. Bauer [Veterinary Record (1990) 127, 353-354] demonstrated an adequate efficacy against Moniezia expensa in lambs at a dose of 3.75mg/kg. Based on this study a praziquantel dose of 3.75mg/kg was chosen.

TRIAL I

Summary

Two groups of milk lambs - slaughter at ten days. The formulation of Example 1 at a dose of 2ml/10kg of body weight.

| | | |
|---|---|---|
| epg Reduction % Strong Nem. | Formulation of Example 1 | Control |
| | 98% | (800%) |
| % Reduction worm counts versus controls | Haemonchus spp | 100% |
| | Ostertagia spp | 97% |
| | Nematodirus spp | 100% |
| | Trichostrongylus spp | 100% |
| | Cooperia | 100% |
| | Moniezia | |
| | Scoleces | 100% |
| | Segments | 98% |

A high level of efficacy was demonstrated by the formulation of Example 1 against roundworms and tapeworms.

TRIAL REPORT I

OBJECTIVE

To assess by dosing and slaughter trial the efficacy and dose compatibility of the formulation of Example 1 on lambs in the control of tapeworm and roundworm.

MATERIALS The formulation of Example 1

TRIAL DESIGN

Two groups of lambs were divided into two random groups as follows:

Group 1 Dosed with the formulation of Example 1

Dose rate 2 ml/10kg bodyweight
Lambe Nos. 43, 42, 55, 23, 14, 61, 45, 47

All lambs were tagged, weighed and faecal sampled predosing.
All lambs were slaughtered at 10 days post treatment and tapeworm and nematode worm counts done on the abomasum and small intestine.

Reaction of animals at drenching observed and no effects noticed

| | | | EGGS/GRAM | | | | | 10 DAY CRITICAL SLAUGHTER WORM COUNTS | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tag No. | Wgt. kgs | Dose ml | Strong. | Nem. | Strong. | Nem. | Haem. | Ostert. | Trich. | Nema. | Trich. | Coop. | MONIEZIA Scolex | MONIEZIA Segments ml. |
| GROUP 1 - LEVITAPE 4ml/10kg | | | | | | | | | | | | | | |
| 43 | 22 | 8.8 | 250 | – | – | – | – | 500 | – | – | – | – | . | – |
| 42 | 24 | 9.6 | 50 | – | – | – | – | – | – | – | – | – | . | – |
| 55 | 20 | 8.0 | 350 | – | – | – | – | 200 | – | – | – | – | . | – |
| 23 | 15 | 6.0 | 650 | – | – | – | – | – | – | – | – | – | . | – |
| 14 | 16 | 6.4 | 2200 | – | – | – | – | 400 | – | – | – | – | . | – |
| 61 | 17 | 6.8 | 300 | – | – | – | – | – | – | – | – | – | . | – |
| 45 | 22 | 8.8 | 250 | – | – | – | – | – | – | – | – | – | . | 5 |
| 47 | 19 | 7.6 | 200 | – | 50 | – | – | – | – | – | – | – | . | – |
| MEAN | | | 531.2 | – | 6.2 | – | – | 137.5 | – | – | – | – | . | 0.6 |
| GROUP 2 - CONTROL | | | | | | | | | | | | | | |
| 37 | 20 | – | 1650 | – | 3750 | – | 150 | 14000 | – | 200 | 2200 | 400 | 8 | 3 |
| 20 | 16 | – | 1000 | – | 2800 | – | 250 | 1400 | – | – | 1000 | 200 | 8 | 100 |
| 5 | 26 | – | 900 | – | 1400 | – | 40 | 6000 | – | – | 2800 | 400 | 3 | 1 |
| 11 | 19 | – | 600 | – | 950 | – | 180 | 800 | – | – | 600 | 200 | . | – |
| 17 | 20 | – | 800 | – | 2650 | – | 70 | 3000 | – | 100 | 700 | 500 | 2 | 8 |
| 63 | 17 | – | 400 | – | 2400 | – | 140 | 5800 | – | 100 | 2000 | 800 | 2 | 45 |
| 51 | 18 | – | 100 | – | 950 | – | 10 | 1800 | – | 100 | 600 | 100 | 2 | 60 |
| 32 | 18 | – | 200 | – | 450 | – | 30 | 2400 | – | – | 600 | 200 | 2 | 35 |
| MEAN | | | 691.2 | – | 6166.7 | – | 678 | 4375 | – | 62.5 | 1275 | 350 | 3.3 | 31.5 |

The tabulated results above show for each result the weights of the lambs, the dose administered, the faecal egg counts predosing and the 10 day worm counts. The efficacy of the formulation of Example 1 on Moniezia expansa is demonstrated. The levamisole shows no diminution in its efficacy on the common nematodes in lambs.

**TRIAL II**

Summary

Three groups of lambs - slaughter at ten days.

Group 1 Formulation of Example 1 - 1ml/5kg
Group 2 Albendazole - 1ml/5kg
Group 3 Control - untreated

| % epg Reduction | | Formulation of Example 1 | Albendazole | Control |
|---|---|---|---|---|
| Strong | | 15% | 45% | (788%) |
| Nem | | 100% | + | + |
| % Reduction worm counts versus controls | Haemonchus spp | | 60% | 30% |
| | Ostertagia spp | | 82% | 96% |
| | Nematodirus spp | | 85% | (23%) |
| | Trichostrongylus spp | | 100% | 25% |
| | Cooperia spp | | - | - |
| | Moniezia | | | |
| | Scoleces | | 99% | 19% |
| | Segments | | 100% | 23% |

Clear evidence of resistant nematodes to levamisole and albendazole.
Albendazole resistant moniezia were cleared by the formulation of Example 1.

TRIAL REPORT II

237086

OBJECTIVE

To assess by dosing and slaughter trial the efficacy and dose compatibility of the formulation of Example 1 on lambs in the control of tapeworm and roundworm.

MATERIALS

1. Formulation of Example 1
   8mg/kg levamisole/3.75 mg/kg praziquantal
2. Albendazole

TRIAL DESIGN

Three groups of lambs were divided into three random groups as follows:

Group 1 - 8 Lambs, Group 2 - 8 Lambs, Group 3 - 7 Lambs.

Group 1

Dosed with the formulation of Example 1
(3.75 mg/kg praziquantal)
(8mg/kg levamisole)

Dose rate 1 ml/1 kg bodyweight
Lamb Nos. 50, 54, 37, 75, 35, 35, 30, 61, 52

Group 2

Albendazole 1ml/5kg
Lamb Nos. 48, 64, 56, 33, 60, 58, 44, 59

Group 3

Control
Lamb Nos. 40, 32, 57, 49, 43, 46, 51

All lambs were tagged, weighed and faecal sampled predosing.
All lambs were slaughtered at 10 days post treatment and tapeworm and nematode worm counts done on the abomasum and small intestine.

Reaction of animals at drenching observed and no effects noticed.

| Tag No. | Wgt. kgs | Dose ml | EGGS/GRAM Strong. | EGGS/GRAM Nem. | 10 DAY CRITICAL SLAUGHTER WORM COUNTS Haem. | Ostert. | Trich. | Nema. | Trich. | Coop. | MONIEZIA Scolex | MONIEZIA Segments ml. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GROUP 1 - LEVITAPE II (1ml/5kg) | | | | | | | | | | | | |
| 50 | 16 | 3.0 | 1900 | 100 | – | – | – | 100 | – | 100 | – | – | – | – |
| 54 | 14 | 3.0 | 50 | – | – | – | – | – | – | 30 | – | – | – | – |
| 37 | 14 | 3.0 | 450 | – | – | – | – | – | – | – | – | – | – | – |
| 75 | 13 | 3.0 | 600 | – | – | – | – | 10 | – | – | – | – | – | – |
| 35 | 14 | 3.0 | 350 | 50 | 750 | – | – | 200 | – | 100 | – | – | 1 | – |
| 30 | 14 | 3.0 | 900 | – | 2850 | – | 100 | 1900 | – | – | – | – | – | – |
| 61 | 12 | 2.5 | 300 | – | – | – | – | 20 | – | – | – | – | – | – |
| 52 | 26 | 5.0 | 300 | – | | | | Missing | | | | | | |
| MEAN | | | 606.3 | 18.8 | 514 | – | 14.3 | 318.8 | – | 32.8 | – | – | 0.14 | – |
| GROUP 2 - ALBENDAZOLE (1ml/5kg) | | | | | | | | | | | | |
| 48 | 16 | – | 750 | – | 50 | – | 30 | 100 | – | 100 | – | – | 55 | – |
| 64 | 14 | – | – | – | 500 | – | 30 | 100 | – | 20 | – | – | 4 | – |
| 56 | 14 | – | 450 | – | 150 | – | – | – | – | 700 | – | – | 11 | 40 |
| 33 | 13 | – | 150 | – | 400 | – | 20 | – | – | 1000 | 100 | – | 34 | 10 |
| 60 | 14 | – | 2250 | – | 1000 | 200 | 40 | 100 | – | 100 | – | – | 39 | 27 |
| 58 | 14 | – | 900 | – | 700 | 50 | 20 | – | 100 | 100 | – | – | 16 | 14 |
| 44 | 12 | – | 700 | – | 150 | 50 | 100 | 200 | – | 100 | – | – | 29 | 3 |
| 59 | 26 | – | 950 | – | 400 | – | – | – | – | 10 | – | – | 4 | – |
| MEAN | | | 768.7 | – | 418.8 | 37.5 | 30.0 | 62.5 | 12.5 | 266.3 | 112.5 | – | 24.0 | 11.8 |
| GROUP 3 - CONTROL | | | | | | | | | | | | |
| 40 | | | 450 | – | 1350 | – | 40 | 1200 | – | 300 | 100 | – | 24 | 15 |
| 32 | | | 800 | – | 7300 | 500 | 60 | 2500 | – | 400 | 200 | – | 3 | – |
| 57 | | | 500 | – | 950 | 50 | 30 | 1000 | – | 300 | – | – | 18 | 1 |
| 49 | | | – | – | 1750 | 150 | 20 | 400 | – | – | – | – | 52 | 45 |
| 43 | | | 750 | – | 1050 | – | 30 | 3200 | – | 200 | 100 | – | 40 | 30 |
| 46 | | | 450 | – | 13450 | – | 40 | 2200 | – | 100 | 500 | – | 32 | 2 |
| 51 | | | 4000DEAD | | | | | | | | | | | |
| MEAN | | | 485.7 | | 4308.0 | 116.0 | 36.8 | 1750 | – | 216.6 | 150.0 | – | 28.6 | 15.5 |

The tabulated results above show for each result the weights of the lambs, the dose administered, the faecal egg counts predosing and post dosing and the 10 day worm counts. The efficacy of the formulation of Example 1 on Moniezia expansa is demonstrated. The levamisole and albendazole group results shows efficacy on the common nematodes in lambs is not as high as desired as resistance appears to be present to both these actives.

The albendazole was not effective in its efficacy against Monezia expansa. The formulation of Example 1 shows a very successful level of elimination of this tapeworm when in combination with levamisole.

TRIAL REPORT III

LOCATION

OBJECTIVE

To assess by dosing and slaughter trial the efficacy and dose compatibility of the formulation of Example 1 on lambs in the control of tapeworm and roundworm.

MATERIALS

1. The formulation of Example 1 including minerals and trace elements such as copper, cobalt, selenium, iodine and zinc. 8mg/kg levamisole/3.75 mg/kg praziquantal with Minerals
2. Albendazole (Valbazen)

TRIAL DESIGN

Three groups of lambs were divided into three random groups as follows:

Group 1 - 8 Lambs, Group 2 - 8 Lambs, Group 3 - 8 Lambs

Group 1 — Dosed with the formulation of Example 1 including minerals and trace elements such as copper, cobalt, selenium, iodine and zinc. (3.75 mg/kg praziquantal) (8mg/kg levamisole)

Dose rate 1 ml/5 kg bodyweight
Lamb Nos. 17, 20, 23, 33, 36, 37, 102, 108

Group 2 — Albendazole 1ml/5kg
Lamb Nos. 12, 21, 26, 39, 43, 46, 51, 103

Group 3 — Control
Lamb Nos. 10, 11, 18, 32, 41, 49, 105, 109

All lambs were tagged, weighed and faecal sampled predosing. All lambs were slaughtered at 9 days post treatment and tapeworm and nematode worm counts done on the abomasum and small intestine.

Reaction of animals at drenching observed and no effects notice.

| | | | EGGS/GRAM | | | | 10 DAY CRITICAL SLAUGHTER WORM COUNTS | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tag No. | Wgt. kgs | Dose ml | Strong. | Nem. | Strong. | Nem. | Haem. | Ostert. | Trich. | Nema. | Trich. | Coop. | MONIEZIA Scolex | MONIEZIA Segments ml. |
| GROUP 1 - LEVITAPE II (1ml/5kg) | | | | | | | | | | | | | | |
| 17 | 28 | 6.0 | 150 | - | - | - | - | - | - | - | - | - | - | - |
| 20 | 22 | 4.5 | 50 | - | - | - | - | - | - | - | - | - | - | - |
| 23 | 20 | 4.0 | 200 | - | 50 | - | - | - | - | - | - | - | - | - |
| 33 | 26 | 5.0 | - | - | - | - | - | - | - | - | - | - | - | - |
| 36 | 26 | 5.0 | 50 | - | 100 | - | - | - | - | - | - | - | - | - |
| 37 | 24 | 5.0 | 50 | - | 50 | - | - | - | - | - | - | - | - | - |
| 102 | 23 | 4.5 | 200 | - | - | - | - | - | - | - | - | - | - | - |
| 108 | 32 | 6.5 | 50 | - | - | - | - | - | - | - | - | - | - | - |
| MEAN | | | 93.78 | - | 37.5 | - | - | - | - | - | - | - | - | - |

GROUP 2 - ALBENDAZOLE (1ml/5kg)

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | 26 | 5.0 | 50 | – | 5 | – | 160 | – | – | – | – | – | 3 | 10 |
| 21 | 22 | 4.5 | – | – | – | – | 10 | – | – | – | – | – | 5 | – |
| 26 | 28 | 5.5 | 100 | – | – | – | 50 | – | – | – | – | – | – | – |
| 39 | 24 | 5.0 | 100 | – | – | – | 20 | – | – | – | – | – | 1 | – |
| 43 | 26 | 5.0 | 150 | – | 50 | – | – | – | – | – | – | – | 1 | 5 |
| 46 | 30 | 6.0 | – | – | 50 | – | – | – | – | – | – | – | – | 35 |
| 51 | 28 | 5.5 | 100 | – | – | – | – | – | – | – | – | – | – | 5 |
| 103 | 20 | 4.0 | 300 | – | – | – | 450 | – | – | – | – | – | – | – |
| MEAN | | | 100.0 | – | 13.1 | – | 86.3 | – | – | – | – | – | 6.9 | 11.8 |

GROUP 3 - CONTROL

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 22 | 100 | – | 600 | – | 650 | 100 | – | – | 700 | 200 | 6 | 110 |
| 11 | 24 | 250 | – | 2250 | – | 1400 | 400 | – | – | 2200 | 4000 | 2 | 85 |
| 18 | 22 | – | – | 400 | – | 880 | 300 | – | 100 | 1800 | 3200 | 2 | 80 |
| 32 | 30 | 50 | – | – | – | 400 | 600 | – | 100 | 200 | 300 | 8 | 15 |
| 41 | 28 | 100 | – | 50 | – | 50 | 100 | – | – | 200 | – | – | – |
| 49 | 22 | 50 | – | 950 | – | 560 | 200 | – | 100 | – | – | – | – |
| 105 | 24 | 150 | – | 1400 | – | 700 | 100 | – | – | 1600 | 4800 | 2 | 55 |
| 109 | 26 | – | – | 1150 | – | 970 | 200 | – | – | 800 | 1400 | – | 40 |
| MEAN | | 87.5 | – | 850 | – | 701.3 | 250 | – | 37.5 | 937.5 | 1758 | 2.5 | 48.1 |

The tabulated results above show for each result the weights of the lambs, the dose administered, the faecal egg counts predosing and post dosing and the 9 day worm counts. The efficacy of the formulation of Example 1 including minerals and trace elements on Moniezia expansa is demonstrated. The albendazole group results shows efficacy on the common nematodes in lambs is not as high as desired as resistance appears to be present to this active for Haemonchus contortus.

The albendazole was not effective in its efficacy against Monezia expansa. The formulation of Example 1 shows a very successful level of elimination of this tapeworm when in combination with levamisole, with no dimunition in efficacy by levamisole against the common nematodes in lambs.

## VARIATIONS



A range of compositions have been described suitable for the treatment or prevention of helminthiasis in sheep and goats. The trials show dose rates of 3.75 mg/kg of praziquantel and 8mg/kg of levamisole. We have discovered that the dose rate of the formulation of Example 1 can be reduced, thereby reducing the dose rate of praziquantel to about 2mg/kg whilst preventing sheep measles in lambs. Preferred dose rates for lambs and sheep are in the range of 2-7.5 mg/kg of live body weight of praziquantel, giving a comparable range of levamisole of 4-16 mg/kg of live body weight.

Any of the avermectins: ivermectin, moxidectin, doramectin, could be replaced by Milbemycin D or other members of the Milbemycin family (Merck Index # 6112, 11th Edition).

Finally it will be appreciated that various other alterations and modifications may be made to the foregoing without departing from the scope of this invention as set forth in the following claims.

**WHAT WE CLAIM IS:**

1. A veterinary liquid anthelmintic composition suitable for administration to farm animals including a liquid carrier and an effective amount of the anthelmintic praziquantel together with an effective amount or amounts of at least one other anthelmintic selected from the group comprising the avermectins; milbemycins; levamisole; tetramisole; or a benzimidazole chosen from the group comprising mebendazole, fenbendazole, oxfendazole, albendazole, cambendazole, parbendazole, oxibendazole, flubendazole or cyclobendazole.

2. A veterinary liquid anthelmintic composition suitable for administration to farm animals as claimed in claim 1 wherein the praziquantel is dissolved in the liquid carrier.

3. A veterinary liquid anthelmintic composition suitable for administration to farm animals as claimed in claim 2 wherein the liquid carrier comprises a mixture of ethanol and propylene glycol.

4. A veterinary liquid anthelmintic composition suitable for administration to farm animals as claimed in claim 1 wherein the praziquantel is suspended in the liquid carrier.

5. A veterinary liquid anthelmintic composition suitable for administration to farm animals as claimed in claim 4 wherein the liquid carrier comprises water and one or more surfactants.

6. A veterinary anthelmintic drench suitable for administration to farm animals including a non-toxic liquid carrier and an effective amount of the anthelmintic praziquantel together with an effective amount or amounts of at least one other anthelmintic selected from the group comprising the avermectins; milbemycins; levamisole; tetramisole; or a benzimidazole chosen from the group comprising mebendazole, fenbendazole, oxfendazole, albendazole, cambendazole, parbendazole, oxibendazole, flubendazole or cyclobendazole.

7. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 6 wherein the praziquantel is dissolved in the liquid carrier.

8. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 6 wherein the praziquantel is suspended in the liquid carrier.

9. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 8 wherein the liquid carrier comprises water and one or more surfactants.

10. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 6 wherein the other anthelmintic is selected from the group comprising the avermectins; milbemycins; levamisole; or tetramisole.

11. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 6 wherein the drench includes levamisole, and the drench has a pH of less than 4.0.

12. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 8 wherein the pH is about 3.0.

13. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 6 wherein the formulation is a drench and contains from 0.5 to 15% w/v of praziquantel.

14. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 10, wherein the formulation contains levamisole hydrochloride from 1 to 10% w/v.

15. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 10, wherein the formulation contains from 0.05 to 1% w/v of ivermectin or moxidectin or doramectin.

16. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 6, wherein the formulation contains from 1-15% w/v of a

benzimidazole chosen from the group comprising mebendazole, fenbendazole, oxfendazole, albendazole, cambendazole, parbendazole, oxibendazole, flubendazole or cyclobendazole.

17. A veterinary anthelmintic drench suitable for administration to farm animals as claimed in claim 1 substantially as herein described with reference to any one of the Examples.

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18. A method for treating helminthiasis in animals with a drench as claimed in any one of claims 4 to 16.

19. A method as claimed in claim 18 wherein the drench is administered to sheep to prevent or control cestodes such as *Moniezia Spp.* or *Taenia ovis*.

20. A method as claimed in claim 18 wherein the drench is administered as a drench having an effective amount of praziquantel in the range of 2 to 7.5 mg/kg of body weight.

21. A method as claimed in claim 18 substantially as herein described with reference to any one of the trials as defined herein.

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